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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/076,204	02/13/2002	Roberto Levi	955-16	8595

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EXAMINER
HENLEY III, RAYMOND J

ART UNIT	PAPER NUMBER
1614	10

DATE MAILED: 08/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/076,204	LEVI ET AL.	
	Examiner	Art Unit	
	Raymond J. Henley III	1614	

-- The MAILING DATE of this communication appears on the c ver sheet with the corresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-30 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-30 is/are rejected.

7)☒ Claim(s) 11-16 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5-7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

CLAIMS 1-30 ARE PRESENTED FOR EXAMINATION

Applicants' Amendment filed May 23, 2002, Response to Restriction Requirement and Preliminary Amendment filed July 18, 2003, Information Disclosure Statement filed May 17, 2002, and Supplemental Information Disclosure Statements filed July 12, 2002 and April 14, 2003 have been received and entered into the application.

Accordingly, the specification at paragraph [0002] and claim 1 have been amended and claims 31 and 32 have been canceled. Also, the Examiner has considered the cited references as reflected by the attached, completed copies of form PTO-1449 (6 pages total).

Restriction Requirement

Applicant's election without traverse of the invention of Group I, claims 1-30 in the Response to Restriction Requirement and the cancellation of claims 31 and 32 are acknowledged.

Insofar as all claims presently are directed to the same invention (for examination purposes), the restriction requirement set forth in the Office action dated June 18, 2003 is **withdrawn**.

Claim Objections

Claims 11-16 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim.

In claim 11, which depends from claim 1, "the H_3R antagonist..." has no antecedent basis.

Claims 12-16 are directed to therapeutic objectives different from the therapeutic objective of the claim from which they ultimately depend, i.e., claim 1.

Appropriate correction of the above is required.

In order to expedite prosecution, the Examiner will treat claim 11 as if it depends from claim 10 and will treat claims 12-16 as if they were in proper form and read "The method of claim 1, wherein...***further*** inhibits..." (e.g., for claim 12).

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Silver et al. (Applicants' cit. No. 11, IDS filed July 12, 2002), Mackins et al. (Applicants' cit. No. 5, IDS filed July 12, 2002 "Mackins I"), Mackins et al. (Applicants' cit. No. 4, IDS filed May 17, 2002 "Mackins II"), Levi et al. (Applicants' cit. No. 16, IDS filed May 17, 2002), Imamura et al. (Applicants' cit. No. 15, IDS filed May 17, 2002) and Leurs et al. (Applicants' cit. No. 12, IDS filed May 17, 2002) in view of Applicants' acknowledgement at page 7, paragraph [0029] of the present specification and Avery's (cited by the Examiner).

Silver et al. (see page 2857, the entire text under the heading "Discussion") teach that their results provide a link between H_3 receptors and the Na^+/H^+ exchanger that may limit the excessive release of norepinephrine during protracted myocardial ischemia. (The Examiner notes that the "link" mentioned here is that an H_3 receptor agonist inhibits the Na^+/H^+ exchanger as shown, for example, in this reference at Figure 3, and at page 287, column 1, 1st line above

"Discussion" sets forth that imetit, an H_3 receptor agonist, was 35% effective in antagonizing the activity of the Na^+/H^+ exchanger)(present claim 12). Also, the authors found that H_3 receptor activation (the Examiner notes that this is the activity of an agonist) attenuates carrier-mediated norepinephrine release and attenuates reperfusion arrhythmias. (The Examiner also notes that in this document at page 2855, column 1, first and second sentences under the abstract, it is taught that excessive norepinephrine release from sympathetic nerve endings is associated with myocardial ischemia and infarction and that cardiac dysfunction and arrhythmias ensue therefrom). The authors also report that in previous studies it was shown that activation of the Na^+/H^+ exchanger plays a pivotal role in the Na^+ -dependent carrier mediated norepinephrine release from adrenergic nerve endings that occurs during protracted myocardial ischemia. Modulation of intracellular sodium (present claim 14) is taught at page 2857, column 2, "The ischemia-induced acidosis...leads to excessive accumulation of intracellular Na^+.".

At page 2858, column 2, last paragraph of this reference, it is set forth that "Ischemia-induced acidosis activates NHE, i.e., the Na^+/H^+ exchanger, in cardiac myocytes and NHE inhibitors, i.e., H_3 receptor agonists, are known to provide beneficial anti-ischemic effects, such as reduction in infarct size and reperfusion arrhythmias...[t]his cardioprotection has been attributed to the ability of NHE inhibitors to prevent Ca^+ overload in cardiomyocytes. Indeed, NHE blockade will limit the influx of Na^+, so that less intracellular Na^+ will be available to the Na^+-Ca^+ exchanger and intracellular Ca^+ will accumulate.". (See present claim 16). Finally, relating to this reference, at the last line of column 2, page 2858, it is set forth that "...our findings provide a rationale for the use of selective H_3R agonists to alleviate dysfunctions associated with myocardial ischemia".

The Examiner notes that Mackins I and Mackins II are identical articles. Specific references, i.e., pages, Figures, are made with respect to Mackins I. The Examiner also relies herein on the teachings contained in Mackins II at the page/coloumn/Figure which correspond to the page/column/Figure of Mackins I. Mackins I teach that H_3R agonists inhibit noradrenaline, i.e., norepinephrine, release and should be useful in the treatment of myocardial ischemia and infarction because of their capacity to inhibit NHE, i.e., the Na^+/H^+ exchanger, in adrenergic nerve endings and provide an expectation that such agonists could afford cardioprotective effects, thus attenuating reperfusion injury and improve recovery from left ventricular dysfunction after myocardial infarction. See the last paragraph at pages 4-5, under the heading "Expert Opinion". At column 2 on page 4, it is taught that once released, noradrenaline enhances intracellular calcium. (See present claim 15) In Figure 2B at page 4, it is represented that the NHE modulates sodium influx into a cell and that an H_3R agonist would inhibit the NHE and thus modulate, i.e., decrease, the concentration of intracellular sodium (see present claims 14 and 28). Figure 2B also represents that EIPA, i.e., an H_3R antagonist, inhibits NHE which inhibits the influx of sodium ions into the cell which in turn would inhibit the release of noradrenaline from the cell (see present claims 9, 10 and 27).

Levi et al. in the abstract indicate that H_3R, i.e., histamine type 3 receptors, have been identified as inhibitory heteroreceptors in adrenergic nerve endings of the heart (see present claims 8 and 26). Also in the abstract it is indicated that selective H_3R agonists attenuate carrier-mediated release of noradrenaline, i.e., NE, in both animal and human models of protracted myocardial ischemia. (See present claims 1-3) Further in the abstract, it is indicated that H_3R-mediated attenuation of exocytotic NE release involves an inhibition of N-type Ca^{2+} -channels.

Finally, it is indicated in the abstract that because excess NE release can trigger severe arrhythmias and sudden cardiac death, negative modulation of NE release by H_3R agonists may offer a novel therapeutic approach to myocardial ischemia. (See present claims 1-3).

In Fig. 1 at page 826 of Levi et al., it is represented that the NHE modulates sodium influx into a cell and that an H_3R agonist would inhibit the NHE and thus modulate, i.e., decrease, the concentration of intracellular sodium (see present claims 14 and 28). Fig. 1 also represents that EIPA, i.e., an H_3R antagonist, inhibits NHE which inhibits the influx of sodium ions into the cell which in turn would inhibit the release of noradrenaline from the cell (see present claims 9, 10 and 27). The remainder of Levi et al. (pages 826-829) teaches that which has been taught by the preceding references and thus will not be reiterated for the sake of brevity.

Imamura et al. teach in the abstract that histamine H_3 –receptors downregulate norepinephrine exocytosis, which is markedly enhanced in early myocardial ischemia and the H_3 agonist imetit decreased carrier mediated norepinephrine (NE) release which in turn was blocked by thioperamide. (See present claims 1-4, 10 and 11) At page 479, under the heading "Discussion", the authors further indicate that such a decrease in NE release may be associated with an inhibition of the Na^+/H^+ exchanger. (See present claims12, 13, 19-21 and 27) At the second paragraph under the heading "Discussion", the authors indicate that intracellular sodium is accumulated during ischemia. In the 4^{th} paragraph under the same heading, it is indicated that the selective that histamine H_3 agonist, imetit, markedly attenuated the increase in NE release that occurred during reperfusion after 20-minute global ischemia and thioperamide, an H_3R antagonist, prevented the effect of imetit. (See present claims 1-4, 10, 11, 14 and 28). In the last paragraph of the same section, the authors set forth that histamine H_3 –receptors activation, i.e.,

agonism, attenuates both exocytotic and carrier-mediated norepinephrine release associated with acute and protracted myocardial ischemia, respectively. They further teach that the mechanisms of action are likely to be that the inhibition of exocytosis involves a decreased calcium ion entry via N-type channels (see present claim 16) whereas inhibition of carrier-mediated NE release probably involves an antagonism of the Na^+/H^+ exchanger (see present claims 12, 13, 16 and 19).

The Hatta et al. (Applicants' cit. No. 4, IDS filed July 12, 2002) and Silver et al. (Applicants' cit. No. 11, IDS filed May 17, 2002) have not been relied upon here because the teachings contained therein are no more than cumulative of the above teachings.

At page 3, Figure 3 and under the discussion headed by "H_3 receptors", Leurs et al. teach that thioperamide and clobenpropit were antagonists at the H_3 receptor site (these compounds set forth in present claim 11).

The differences between the above and applicants' claimed subject matter lie in that the references fail to highlight:

(1) each of the agonists as in present claims 4 and 22;

(2) the timing of administration as in present claims 5 and 23;

(3) the physiological characteristics of the agonists as in present claims 6, 7, 24 and 25; and

(4) the additional administration of one or more of the following: a β-blocker, a Ca^{2+} -channel blocker, an anti-arrhythmic, an ACE inhibitor and an angiotensin receptor antagonist as in present claims 17, 18, 29 and 30.

However, the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains because:

(1) At page 7, paragraph [0029] of the present specification, Applicants' acknowledge each of R-(α)-methylhistamine, imetit, immepip, immepyr, 4-(1H-4-imidazolylmethylene) 1-methylpiperidine, S-α-chloromethylhistamine, cyclopropylhistamine, SKF 91606, Sch 50971, VUF 4864 as being known histamine H_3 receptor agonists.

(2) The determination of the optimum timing of administration for the treatment of a patient who has suffered myocardial infarction and/or myocardial infarction would have been a matter well within the purview of the skilled artisan who would have been motivated to do so in order to provide such a patient with the most effective therapy as soon as possible in order to prevent further damage or death.

(3) The physiological characteristics of the drug are inherently possessed by the drugs and therefore, whether reported in the literature or not, would have been possessed by the drugs presently claimed.

(4) Avery's shows at page 611, col. 2, section 4.3.3 that calcium antagonists are useful in the treatment of angina which is the pain caused by ischemia. Also, at page 618, sections 5.2.1 and 5.2.2, it is taught that antiarrhythmic drugs and β-blockers would be useful in the treatment of patients who have suffered a myocardial infarction which would have motivated the skilled artisan to employ such drugs with the agonists of the primary references. Also, ACE inhibitors and angiotensin receptor antagonists were well known to be useful for mitigating the effects of angiotensin, i.e., vasodilators. As such, these types of drugs would have been found to be useful

in patients suffering from ischemic conditions which result from insufficient blood flow to the affected organ, i.e., the heart.

Further, it has been held that it is considered prima facie obvious to have combined two or more ingredients each of which was known to be useful for the same purpose in order to form a third composition that is useful for the very same purpose. The idea for combining them flows logically from their have been used separately. See In re Kerkhoven 205 U.S.P.Q. 1069 (CCPA 1980) and the cases cited therein. The skilled artisan would have been motivated to combine the above agents in order to achieve at least additive results and to provide the individual being treated with the most convenient, effective therapy possible.

Accordingly, for the above reasons, the claims are deemed properly rejected and none of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Raymond J. Henley III whose telephone number is 703-308-4652. The examiner can normally be reached on M-F, 8:30 am to 4:00 pm Eastern Time.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel can be reached on 703-308-4725. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Raymond J. Henley III
Primary Examiner
Art Unit 1614